Glossary of acronyms listed in alphabetical order

BDNF: brain-derived neurotrophic factor	HPA: hypothalamic-pituitary-adrenal axis
CAM: complementary and alternative medicine	HPT: hypothalamic–pituitary–thyroid
CBT: cognitive behavioural therapy	M1: motor cortex
CPAP: continuous positive airway pressure	NIBS: non-invasive brain stimulation
DLPFC: dorsolateral prefrontal cortex	OSA: obstructive sleep apnea
EEG: electroencephalography	rTMS: repetitive transcranial magnetic stimulation
EPM: endogenous pain modulation	tDCS: transcranial direct current stimulation
GABA: γ-aminobutyric acid	

1. Introduction

Sleep disturbances and chronic pain often co-exist, with insomnia and obstructive sleep apnea (OSA) being the most commonly diagnosed sleep conditions [88]. Individuals with chronic pain present poorer and more disturbed sleep than healthy controls, with reduced sleep quality and efficiency, longer sleep onset latency, and increased wake after sleep onset [9]. Previous hypotheses have emphasized a bidirectional relationship between sleep and pain, with poor sleep increasing pain, and pain disturbing sleep. However, the influence of poor sleep on chronic pain has received more robust empirical support [4]. These effects may vary depending on pain populations and the presence of other comorbidities. Presented independently or jointly, disturbed sleep and chronic pain have a significant impact on patients' well-being, ability to function, and quality of life [1; 35; 58].

A number of different management strategies are available to improve sleep disturbances or chronic pain disorders via disrupting the vicious cycle formed by co-existing sleep and pain problems, and promoting a situation in which an improvement in one condition may lead to an improvement in the other one). However, sleep disturbances and chronic pain are often targeted

independently, with a failure to take a more holistic approach that is based on symptoms rather than on the possible underlying mechanisms. This can increase polypharmacy and its associated risks such as increased side-effects and the aggravation of other conditions [61; 132]. Moreover, the heterogeneity in the clinical presentation of this interaction between sleep and pain and the considerable variability in treatment responses among these individuals, may suggest the presence of different pathways and pathophysiological subtypes related to insomnia and OSA.

Classifying individuals according to different phenotypes (i.e., observable characteristics, traits, or clinical presentations without mechanism implication) and ultimately to endotypes (i.e., subtype of a disease condition, implying distinct pathophysiological mechanisms) can help to characterize diseases and select more targeted therapeutic approaches, especially in the era of precision medicine. Some examples can be observed in the fields of OSA [18; 74], chronic rhinosinusitis [19] or asthma [71], where different endotypes have been identified to suggest different treatment strategies. The identification and grouping of phenotypic vulnerabilities in individuals with sleep and pain problems obtained through clinical and physiological tests may help discover disease subtypes or endotypes involving different mechanisms and pathways. It is possible that insomnia and OSA present different pathways in their relation to pain. Therefore, different genetic/demographic (sex, age, ethnicity related), behavioural (wake, emotional and sleep related) and possibly physiological (sleep related) phenotypic characteristics could be used to recognize insomnia or OSA among individuals with chronic pain [55; 74; 75; 123] (Figure 1). Consequently, different management strategies could be selected to target more adequately the underpinning putative mechanisms of this interaction. Although these concepts still need to be further investigated, the identification of predominant pathways in each sleep disorder could be a first step towards the definition of endotypes.

One barrier to this approach is the fact that the exact mechanisms underlying the associations between these sleep disorders and chronic pain have not yet been fully elucidated. However, different putative mechanisms have been proposed to mediate the relationship between sleep disturbances and chronic pain, with four of them being better supported by evidence (Figure 1). One proposed mechanism is endogenous pain modulation (EPM) alteration. Research has shown that sleep deprivation, which can occur in both insomnia and OSA, can amplify pain signals by altering EPM processes such as decreasing pain inhibition or pain habituation, or increasing pain facilitation [38; 122; 124; 126]. Another putative mechanism associated with both insomnia and OSA is the dysregulation of the autonomic system. It has been shown that sleep deprivation can increase sympathetic drive via the sympathoadrenal system and the hypothalamic-pituitary adrenal axis [92], which could contribute to an increase in nociceptive signals [11]. At the same time, pain can increase sympathetic cardiovascular activation [21; 84] and reduce sleep efficiency, thus causing lighter sleep and more arousals, which would increase pain sensitivity and consequently reinforce the vicious cycle between sleep disturbances and chronic pain [116]. Mood disorders, such as depression and anxiety, and negative affect could also be a possible mechanism. They are more frequently observed in insomnia, and could also mediate the relationship between sleep and pain [45; 121; 142]. For instance, negative mood/affect may increase physiologic or cognitive arousal while in bed or during the day, increasing hypervigilance and attentional-reward biases (e.g., increase the tendency to selectively attend to pain), which can consequently disturb sleep and increase pain [46; 111]. Moreover, negative mood/affect can dysregulate diurnal patterns, decreasing physical and social activities during the day, and increasing time in bed ‘‘resting’’ or engaging in non-sleep activities [106], thus impairing normal sleep. Mood, sleep disturbances, and pain can affect each other, further perpetuating the vicious cycle [106]. Finally, another suggested mechanism is the presence of systemic inflammation caused by sleep fragmentation in insomnia and OSA and/or hypoxia in OSA, which can facilitate pain signaling [13].

In this topical review we aim to describe and assess management strategies that can simultaneously target the interaction between sleep and pain problems through different mechanisms or pathways, and propose future directions towards the development of putative endotypes. Treatments for OSA such as continuous positive airway pressure (CPAP) and oral appliances will not be discussed due to the limited evidence in relation to their use and pain improvement, although they can be combined with the options described below.

2. Pharmacological approaches

Pharmacotherapy is a common approach to manage chronic pain and sleep conditions such as insomnia. Although evidence supporting the use of long-term medication is limited, some drugs can aid in the disruption of the vicious cycle between sleep disturbances and chronic pain in the short-term. Medications directed to treat pain can indirectly help sleep and vice versa. However, those that can target both sleep and pain problems more comprehensively via different pathways become highly appealing. For example, antiseizure medications such as gabapentinoids (e.g., gabapentin, pregabalin) are widely used to manage neuropathic pain or fibromyalgia [25; 47]. By acting at the dorsal root ganglion, the dorsal horn neuron level, and perhaps at the supra-spinal neuron level, gabapentinoids most likely produce analgesia by inhibiting descending serotonergic facilitation and stimulating noradrenergic descending inhibition [70]. Moreover, they have anti-inflammatory properties and can influence the affective component of pain, which are possible underlying mechanisms of the interaction between sleep and pain problems [53; 128; 143]. At the same time, they have independent effects on sleep, not only by enhancing slow-wave sleep, improving sleep stability and decreasing spontaneous arousal [81; 119], but also by reducing anxiety [62]. Nonetheless, they can aggravate OSA, particularly in males [113]. Therefore, while the use of gabapentinoids can be considered in chronic pain individuals with co-existent insomnia due to its impact on EPM, inflammatory, and mood pathways, their use should be avoided in OSA (Figure 1). Cyclobenzaprine [96; 134],

topiramate [99; 145; 146], duloxetine [20; 67; 83], cannabinoids [9; 24; 69] and sodium oxybate [125] are alternatives, but with less empirical support, to manage both sleep disorders and chronic pain. Although trazodone might not have any direct analgesic effect, it can increase sleep arousal thresholds and improve mood, being useful in hyperarousal and mood related pathways [48; 74; 133]. Importantly, the combination of opioids or gabapentin with benzodiazepines should be avoided in individuals with sleep disturbances and OSA due to opioid-related breathing risks [113; 137]. More research assessing the effects of the aforementioned medications is needed to adequately evaluate their benefits in populations in which sleep disturbances and chronic pain co-exist and to assess their efficacy in different subgroups.

3. Non-pharmacological approaches. These include treatments such as cognitive behavioural therapy (CBT), physical therapy, complementary and alternative medicine (CAM), and non-invasive brain stimulation (NIBS). They present minimal side-effects and can complement each other and pharmacological therapies, potentially having a synergic effect. However, despite some initial evidence suggesting their possible benefits, most of these treatments – with the exception of CBT - lack strong evidence supporting their use in co-existing sleep and pain problems. While most of them are considered adjuvant therapies, endotyping strategies could maximize their potential effectiveness (Figure 1).

3.1. Hybrid CBT. CBT is an evidence-based therapy designed to target individuals' maladaptive cognitions, emotions, and behaviours [10]. CBT was initially designed to treat mental health problems such as anxiety and depression, but it has become an important tool to manage other conditions such as insomnia [97] and chronic pain [37]. Indeed, CBT for insomnia (CBT-I) is a first line option in the management of insomnia, having minimal side-effects and demonstrating maintained improvements [135; 144]. In chronic pain, CBT can reduce emotional disturbances, maladaptive behaviours, and also decrease pain and pain interference [98].

Furthermore, CBT-I, sleep hygiene, and psychoeducation have been shown to be effective in improving sleep, pain, and mood symptoms in chronic pain populations with insomnia [129]. In this context, a hybrid CBT approach combining CBT-I components with interventions targeting the cognitive-behavioural aspects of chronic pain has emerged as a promising intervention to better tackle sleep and pain problems [44; 130; 131]. Dissemination of CBT approaches (particularly the training of therapists to be highly skilled in the provision of both sleep and pain treatment) can be costly [89; 101]. These issues could be mitigated through the use of internet-based and home-based CBT, which have been implemented with high rates of success and acceptability [12; 15; 115; 149]. Hybrid CBT programs include general sleep and pain education, sleep restriction therapy, stimulus control for sleep and pain, sleep hygiene instructions, cognitive therapy specific to sleep and pain thinking, relaxation/stress management, and cognition-targeted exercise therapy [104; 130]. Thus, hybrid CBT can help individuals with insomnia and co-existing chronic pain, especially when mood disturbances and hyperarousal mechanisms are present, by improving cognitive (e.g., catastrophizing, anticipation), affective, perceptive and coping skills associated with both sleep disturbances and chronic pain [16; 22; 39; 49; 91] (Figure 1).

3.2. Physical therapy. The benefits of physical activity and exercise in individuals with chronic pain are well-documented [32; 51]. It is thought that physical activity/exercise can have anti-inflammatory effects, reinforce neuromuscular function, and regulate autonomic function through hypothalamic-pituitary-adrenal axis (HPA) activity [54]. In addition to reducing obesity (a major risk factor for insomnia, OSA and chronic pain) physical activity/exercise can increase EPM analgesia by releasing endogenous opioids associated with transient and sometimes long-lasting anti-nociception states, decreasing pain intensity and improving physical function [51] (Figure 1). Moreover, positive effects on sleep related outcomes have been documented with aerobic exercise, possibly due to the release of neurotransmitters such as serotonin or brain-

derived neurotrophic factor (BDNF), which can cause anxiolytic or antidepressant effects [42; 110; 136; 147]. However, these effects seem to be modest [41]. Importantly, exercise needs to be tailored to each individuals' preferences, limitations, and pain conditions, as some may present sensitivity to physical activity [93]. Furthermore, the effects of exercise therapy on sleep in individuals with chronic pain are small [51; 87], possibly requiring more specific sleep-targeted interventions such as CBT-I.

3.3. CAM. This term refers to medical products and practices that are not part of standard medical care. Several CAM strategies can be useful (especially as adjuvant therapies) in sleep disturbances and chronic pain. Mind-body therapies such as meditation, yoga, mindfulness, or hypnosis [2; 76] [73; 120; 141], music therapy [14; 68], acupuncture [23; 100; 150], aromatherapy [60; 72], and in a reduced way supplementation with magnesium, melatonin, or vitamin D [29; 30; 39; 55; 56; 68; 150] have been associated with certain improvements in sleep quality and chronic pain and have the potential to affect different pathways (Figure 1). However, evidence supporting their use in the multimorbidity formed by sleep disturbances and chronic pain is limited in general, and more high-quality research is needed to evaluate their potential properly.

3.4. NIBS. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are safe NIBS techniques that can increase/decrease cortical function and "activate" or "inhibit" different brain networks. rTMS can depolarize neurons through magnetic fields, being mostly known for refractory depression management. However, rTMS is also effective in improving chronic pain outcomes [59; 77; 107]. rTMS analgesic effects are mainly obtained when the motor cortex (M1) is stimulated with high frequencies, by activating thalamocortical pathways and brain areas involved in pain processing such as the insula, anterior, and cingulate cortices; the putamen; the periaqueductal gray matter [34]; and the γ-aminobutyric acid (GABA) and glutamatergic systems [64]. Moreover, M1 stimulation has

been associated with enhanced sleep quality [103; 112], possibly secondarily to pain improvement, but perhaps due to stimulation of distant sleep involved networks [56]. However, it appears that targeting the left dorsolateral prefrontal cortex (LDLPC) with low frequencies is more appropriate in the management of insomnia, as it can balance autonomic function via downregulation of the HPA and hypothalamic–pituitary–thyroid (HPT) axes, reduce cortical arousal levels [26; 103] and induce the release of melatonin, BDNF and GABA, which are important neurotransmitters involved in sleep [43; 63; 127] and analgesia [31; 40; 65]. Moreover, research has shown that high frequency stimulation protocols targeting the DLPC can increase serotonin and dopamine release, potentially restoring defective brain networks present in individuals with sleep deprivation [139], chronic pain [82] and depression [27]. Therefore, dual rTMS stimulation of the M1 and LDLPC could potentially target the multimorbidity formed by sleep and pain problems from different angles by regulating sympathetic function, improving mood, and increasing pain inhibition (Figure 1). Additionally, rTMS also showed to improve airflow dynamics in OSA individuals through the stimulation of airway dilator muscles during sleep. However, evidence is still initial [57; 102].

tDCS is another NIBS technique based on electrical currents that can decrease chronic pain with anodal protocols over the M1, although with less robust evidence [59; 78; 107]. tDCS stimulation of the M1 can increase excitatory postsynaptic potential (129), reverse abnormalities in brain activity and physiology, and possibly enhance endogenous pain modulation networks (30). Moreover, tDCS may improve pain system function through direct effects on the motor, somatosensory, and frontal cortices associated with pain sensitivity [3; 78]. In addition, stimulation of the M1 and DLPFC with tDCS can modify electroencephalographic (EEG) measures, potentially affecting vigilance and promoting sleepiness by enhancing theta and alpha activity during the wake or slow-wave sleep activity [6; 36]. Moreover, it seems that tDCS can mimic or boost slow oscillations and sleep spindle activity, thereby facilitating processes of

sleep-dependent memory consolidation [85; 86]. While there is some evidence showing benefits in respect of both sleep and pain when the M1 is stimulated in chronic pain conditions [3; 66; 118], without appropriately designed studies and mediation analyses it is difficult to determine whether the improvements are the direct result of the stimulation or are secondary to the improvement of pain [56].

Other NIBS techniques with possible potential are transcranial alternating current stimulation [7; 140], transcranial random noise stimulation [29; 50; 108], and acoustic slow wave enhancement with pink noise [33; 109], although evidence supporting their use is still scarce or non-existent in individuals with comorbid sleep and pain problems.

In short, although evidence for using NIBS (specially rTMS) in individuals suffering from sleep and pain problems is growing, more research is required before their use can be recommended.

5. Future directions.

While there is a significant amount of literature on both sleep disorders and chronic pain separately, there is a need for more observational and experimental studies focused on populations where both co-exist to better understand this complex relationship. Studies designed to identify clusters of individuals according to common phenotypic vulnerabilities or clinical characteristics and to grasp the dynamic features of this interaction are needed. Understanding the pathophysiological mechanisms of this interaction is essential to being able to select the best possible treatments, and the development of new ones. Machine learning methods and artificial intelligence algorithms will play a critical role in phenotyping and endotyping this multimorbidity and help to close gaps in current knowledge [52] (Figure 2) using big data collected from a variety of sources including : a) polysomnography to derive macroscopic (from hypnogram), mesoscopic (from EEG) and microscopic (from slow waves or

spindles) indexes [5; 17; 80]; b) autonomic function tests such as cardiovascular reflexes, heart rate variability, catecholamine measurements or sudomotor function during sleep or wake [90; 117]; c) cortical excitability measurements using TMS or electrophysiological methods [138]; d) EPM and somatosensory function testing such as conditioned pain modulation, temporal summation, offset analgesia, and quantitative sensory testing [8; 28; 79; 94; 95; 148]; and e) brain imaging characteristics and networks (functional magnetic resonance imaging) [30], can help us to identify clusters and phenotype individuals suffering from sleep and pain disorders more precisely and develop “signatures” to recognize endotypes. The investigation of treatment response predictors/determinants to NIBS [105; 151] and non-specific effects, can assist in tailoring even more precise treatment strategies to treat individuals according to their specific needs. Likewise, the exciting field of epigenetics allows the monitoring of possible treatment effects at the level of gene expression, holding great potential for endotyping individuals [114].

Figure 1. Phenotypic vulnerabilities of insomnia and obstructive sleep apnea in chronic pain individuals and putative pathways of this relationship to be approached with multitarget strategies.

Legends. Treatment strategies supported by more evidence are represented by thicker continuous lines, while the ones with less evidence are thinner and discontinuous. Abbreviations: BMI: body mass index; OSA: obstructive sleep apnea; NIBS: non-invasive brain stimulation; CBT: cognitive behavioural therapy.

Figure 2. Conceptual design illustrating how machine learning methods and artificial intelligence algorithms can be used to phenotype, endotype, and select treatment avenues in the multimorbidity formed by sleep disturbances and chronic pain.

Legend. Numbers represent machine learning and artificial intelligence methods and do not have any other specific connotation.

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Reference(s):

[1] Afolalu EF, Ramlee F, Tang NKY. Effects of sleep changes on pain-related health outcomes in the general population: A systematic review of longitudinal studies with exploratory meta-analysis. Sleep medicine reviews 2018;39:82-97.

[2] Aggarwal VR, Fu Y, Main CJ, Wu J. The effectiveness of self-management interventions in adults with chronic orofacial pain: A systematic review, meta-analysis and meta-regression. European journal of pain 2019;23(5):849-865.

[3] Ahn H, Sorkpor S, Miao H, Zhong C, Jorge R, Park L, Abdi S, Cho RY. Home-based self-administered transcranial direct current stimulation in older adults with knee osteoarthritis pain: An open-label study. Journal of neuroengineering and rehabilitation 2019;66:61-65.

[4] Andersen ML, Araujo P, Frange C, Tufik S. Sleep Disturbance and Pain: A Tale of Two Common Problems. Chest 2018;154(5):1249-1259.

[5] Andrillon T, Solelhac G, Bouchequet P, Romano F, Le Brun MP, Brigham M, Chennaoui M, Leger D. Revisiting the value of polysomnographic data in insomnia: more than meets the eye. Sleep medicine 2020;66:184-200.

[6] Annarumma L, D'Atri A, Alfonsi V, De Gennaro L. The Efficacy of Transcranial Current Stimulation Techniques to Modulate Resting-State EEG, to Affect Vigilance and to Promote Sleepiness. Brain sciences 2018;8(7).

[7] Arendsen LJ, Hugh-Jones S, Lloyd DM. Transcranial Alternating Current Stimulation at Alpha Frequency Reduces Pain When the Intensity of Pain is Uncertain. J Pain 2018;19(7):807-818.

[8] Arendt-Nielsen L. Central sensitization in humans: assessment and pharmacology. Handbook of experimental pharmacology 2015;227:79-102.

[9] Babson KA, Sottile J, Morabito D. Cannabis, Cannabinoids, and Sleep: a Review of the Literature. Current psychiatry reports 2017;19(4):23.

[10] Beck JS. Cognitive behavior therapy: Basics and beyond: Guilford press, 2011.

[11] Benarroch EE. Pain-autonomic interactions. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2006;27 Suppl 2:S130-133.

[12] Berube M, Gelinas C, Feeley N, Martorella G, Cote J, Laflamme GY, Rouleau DM, Choiniere M. A Hybrid Web-Based and In-Person Self-Management Intervention Aimed at Preventing Acute to Chronic Pain Transition After Major Lower Extremity Trauma: Feasibility and Acceptability of iPACT-E-Trauma. JMIR Form Res 2018;2(1):e10323.

[13] Besedovsky L, Lange T, Haack M. The Sleep-Immune Crosstalk in Health and Disease. Physiological reviews 2019;99(3):1325-1380.

[14] Bradt J, Dileo C, Magill L, Teague A. Music interventions for improving psychological and physical outcomes in cancer patients. The Cochrane database of systematic reviews 2016(8):CD006911.

[15] Buhrman M, Syk M, Burvall O, Hartig T, Gordh T, Andersson G. Individualized Guided Internet-delivered Cognitive-Behavior Therapy for Chronic Pain Patients With Comorbid Depression and Anxiety: A Randomized Controlled Trial. Clin J Pain 2015;31(6):504-516.

[16] Burns JW, Nielson WR, Jensen MP, Heapy A, Czlapinski R, Kerns RD. Specific and general therapeutic mechanisms in cognitive behavioral treatment of chronic pain. Journal of consulting and clinical psychology 2015;83(1):1-11.

[17] Caravan B, Hu L, Veyg D, Kulkarni P, Zhang Q, Chen ZS, Wang J. Sleep spindles as a diagnostic and therapeutic target for chronic pain. Molecular pain 2020;16:1744806920902350.
[18] Carberry JC, Amatoury J, Eckert DJ. Personalized Management Approach for OSA. Chest 2018;153(3):744-755.
[19] Cardell LO, Stjarne P, Jonstam K, Bachert C. Endotypes of chronic rhinosinusitis: Impact on management. J Allergy Clin Immunol 2020;145(3):752-756.
[20] Carter NJ, McCormack PL. Duloxetine: a review of its use in the treatment of generalized anxiety disorder. CNS Drugs 2009;23(6):523-541.
[21] Chen H, Nackley A, Miller V, Diatchenko L, Maixner W. Multisystem dysregulation in painful temporomandibular disorders. J Pain 2013;14(9):983-996.
[22] Cheung JMY, Jarrin DC, Ballot O, Bharwani AA, Morin CM. A systematic review of cognitive behavioral therapy for insomnia implemented in primary care and community settings. Sleep medicine reviews 2019;44:23-36.
[23] Chiu HY, Hsieh YJ, Tsai PS. Systematic review and meta-analysis of acupuncture to reduce cancer-related pain. Eur J Cancer Care (Engl) 2017;26(2).
[24] Choi S, Huang BC, Gamaldo CE. Therapeutic Uses of Cannabis on Sleep Disorders and Related Conditions. J Clin Neurophysiol 2020;37(1):39-49.
[25] Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. The Cochrane database of systematic reviews 2017;1:CD012188.
[26] Cortoos A, Verstraeten E, Cluydts R. Neurophysiological aspects of primary insomnia: implications for its treatment. Sleep medicine reviews 2006;10(4):255-266.
[27] Cowen PJ, Browning M. What has serotonin to do with depression? World Psychiatry 2015;14(2):158-160.
[28] Cruz-Almeida Y, Fillingim RB. Can quantitative sensory testing move us closer to mechanism-based pain management? Pain medicine 2014;15(1):61-72.
[29] Curatolo M, La Bianca G, Cosentino G, Baschi R, Salemi G, Talotta R, Romano M, Triolo G, De Tommaso M, Fierro B, Brighina F. Motor cortex tRNS improves pain, affective and cognitive impairment in patients with fibromyalgia: preliminary results of a randomised sham-controlled trial. Clinical and experimental rheumatology 2017;35 Suppl 105(3):100-105.
[30] Da Silva JT, Letzen JE, Haythornthwaite JA, Finan PH, Campbell CM, Seminowicz DA. Do chronic pain and comorbidities affect brain function in sickle cell patients? A systematic review of neuroimaging and treatment approaches. Pain 2019;160(9):1933-1945.
[31] Danilov A, Kurganova J. Melatonin in Chronic Pain Syndromes. Pain and therapy 2016;5(1):1-17.
[32] Deslandes A, Moraes H, Ferreira C, Veiga H, Silveira H, Mouta R, Pompeu FA, Coutinho ES, Laks J. Exercise and mental health: many reasons to move. Neuropsychobiology 2009;59(4):191-198.
[33] Diep C, Ftouni S, Manousakis JE, Nicholas CL, Drummond SPA, Anderson C. Acoustic slow wave sleep enhancement via a novel, automated device improves executive function in middle-aged men. Sleep 2020;43(1).
[34] DosSantos MF, Ferreira N, Toback RL, Carvalho AC, DaSilva AF. Potential Mechanisms Supporting the Value of Motor Cortex Stimulation to Treat Chronic Pain Syndromes. Frontiers in neuroscience 2016;10:18.
[35] Duenas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. Journal of pain research 2016;9:457-467.
[36] Ebajemito JK, Furlan L, Nissen C, Sterr A. Application of Transcranial Direct Current Stimulation in Neurorehabilitation: The Modulatory Effect of Sleep. Frontiers in neurology 2016;7:54.

[37] Eccleston C, Fisher E, Craig L, Duggan GB, Rosser BA, Keogh E. Psychological therapies (Internet-delivered) for the management of chronic pain in adults. The Cochrane database of systematic reviews 2014(2):CD010152.
[38] Edwards RR, Grace E, Peterson S, Klick B, Haythornthwaite JA, Smith MT. Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. European journal of pain 2009;13(10):1043-1047.
[39] Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. Am Psychol 2014;69(2):153-166.
[40] Enna SJ, McCarson KE. The role of GABA in the mediation and perception of pain. Adv Pharmacol 2006;54:1-27.
[41] Estevez-Lopez F, Maestre-Cascales C, Russell D, Alvarez-Gallardo IC, Rodriguez-Ayllon M, Hughes CM, Davison GW, Sanudo B, McVeigh JG. Effectiveness of exercise on fatigue and sleep quality in fibromyalgia: a systematic review and meta-analysis of randomised trials. Arch Phys Med Rehabil 2020.
[42] Fang YY, Hung CT, Chan JC, Huang SM, Lee YH. Meta-analysis: Exercise intervention for sleep problems in cancer patients. Eur J Cancer Care (Engl) 2019;28(5):e13131.
[43] Feng J, Zhang Q, Zhang C, Wen Z, Zhou X. The Effect of sequential bilateral low-frequency rTMS over dorsolateral prefrontal cortex on serum level of BDNF and GABA in patients with primary insomnia. Brain and behavior 2019;9(2):e01206.
[44] Finan PH, Buenaver LF, Coryell VT, Smith MT. Cognitive-Behavioral Therapy for Comorbid Insomnia and Chronic Pain. Sleep medicine clinics 2014;9(2):261-274.
[45] Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain 2013;14(12):1539-1552.
[46] Finan PH, Remeniuk B. Is the brain reward system a mechanism of the association of sleep and pain? Pain management 2016;6(1):5-8.
[47] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet Neurology 2015;14(2):162-173.
[48] Gaisl T, Haile SR, Thiel S, Osswald M, Kohler M. Efficacy of pharmacotherapy for OSA in adults: A systematic review and network meta-analysis. Sleep medicine reviews 2019;46:74-86.
[49] Geiger-Brown JM, Rogers VE, Liu W, Ludeman EM, Downton KD, Diaz-Abad M. Cognitive behavioral therapy in persons with comorbid insomnia: A meta-analysis. Sleep medicine reviews 2015;23:54-67.
[50] Geiser T, Hertenstein E, Feher K, Maier JG, Schneider CL, Zust MA, Wunderlin M, Mikutta C, Kloppel S, Nissen C. Targeting Arousal and Sleep through Noninvasive Brain Stimulation to Improve Mental Health. Neuropsychobiology 2020:1-9.
[51] Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. The Cochrane database of systematic reviews 2017;4:CD011279.
[52] Goldstein CA, Berry RB, Kent DT, Kristo DA, Seixas AA, Redline S, Westover MB. Artificial intelligence in sleep medicine: background and implications for clinicians. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine 2020;16(4):609-618.
[53] Hayashida KI, Obata H. Strategies to Treat Chronic Pain and Strengthen Impaired Descending Noradrenergic Inhibitory System. International journal of molecular sciences 2019;20(4).
[54] Heijnen S, Hommel B, Kibele A, Colzato LS. Neuromodulation of Aerobic Exercise-A Review. Frontiers in psychology 2015;6:1890.

[55] Herrero Babiloni A, Beetz G, Dal Fabbro C, Martel MO, Huynh N, Masse JF, Sessle B, Lavigne GJ. Dental sleep medicine: Time to incorporate sleep apnoea education in the dental curriculum. European journal of dental education : official journal of the Association for Dental Education in Europe 2020.
[56] Herrero Babiloni A, Bellemare A, Beetz G, Vinet SA, Martel MO, Lavigne GJ, De Beaumont L. The effects of non-invasive brain stimulation on sleep disturbances among different neurological and neuropsychiatric conditions: a systematic review. Sleep medicine reviews 2020:101381.
[57] Herrero Babiloni A, De Beaumont L, Lavigne GJ. Transcranial Magnetic Stimulation: Potential Use in Obstructive Sleep Apnea and Sleep Bruxism. Sleep medicine clinics 2018;13(4):571-582.
[58] Herrero Babiloni A, De Koninck BP, Beetz G, De Beaumont L, Martel MO, Lavigne GJ. Sleep and pain: recent insights, mechanisms, and future directions in the investigation of this relationship. Journal of neural transmission 2020;127(4):647-660.
[59] Herrero Babiloni A, Guay S, Nixdorf DR, de Beaumont L, Lavigne G. Non-invasive brain stimulation in chronic orofacial pain: a systematic review. Journal of pain research 2018;11:1445-1457.
[60] Hwang E, Shin S. The effects of aromatherapy on sleep improvement: a systematic literature review and meta-analysis. Journal of alternative and complementary medicine 2015;21(2):61-68.
[61] Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. J Pharm Pract 2014;27(1):5-16.
[62] Javaherforooshzadeh F, Amirpour I, Janatmakan F, Soltanzadeh M. Comparison of Effects of Melatonin and Gabapentin on Post Operative Anxiety and Pain in Lumbar Spine Surgery: A Randomized Clinical Trial. Anesth Pain Med 2018;8(3):e68763.
[63] Jiang CG, Zhang T, Yue FG, Yi ML, Gao D. Efficacy of repetitive transcranial magnetic stimulation in the treatment of patients with chronic primary insomnia. Cell biochemistry and biophysics 2013;67(1):169-173.
[64] Jodoin M, Rouleau D, Larson-Dupuis C, Gosselin N, De Beaumont L. The clinical utility of repetitive transcranial magnetic stimulation in reducing the risks of transitioning from acute to chronic pain in traumatically injured patients. Prog Neuropsychopharmacol Biol Psychiatry 2017.
[65] Kim JH. Brain-derived neurotrophic factor exerts neuroprotective actions against amyloid beta-induced apoptosis in neuroblastoma cells. Experimental and therapeutic medicine 2014;8(6):1891-1895.
[66] Kim YJ, Ku J, Kim HJ, Im DJ, Lee HS, Han KA, Kang YJ. Randomized, sham controlled trial of transcranial direct current stimulation for painful diabetic polyneuropathy. Annals of rehabilitation medicine 2013;37(6):766-776.
[67] Kluge M, Schussler P, Steiger A. Duloxetine increases stage 3 sleep and suppresses rapid eye movement (REM) sleep in patients with major depression. Eur Neuropsychopharmacol 2007;17(8):527-531.
[68] Kohler F, Martin ZS, Hertrampf RS, Gabel C, Kessler J, Ditzen B, Warth M. Music Therapy in the Psychosocial Treatment of Adult Cancer Patients: A Systematic Review and Meta-Analysis. Frontiers in psychology 2020;11:651.
[69] Kuhathasan N, Dufort A, MacKillop J, Gottschalk R, Minuzzi L, Frey BN. The use of cannabinoids for sleep: A critical review on clinical trials. Exp Clin Psychopharmacol 2019;27(4):383-401.
[70] Kukkar A, Bali A, Singh N, Jaggi AS. Implications and mechanism of action of gabapentin in neuropathic pain. Arch Pharm Res 2013;36(3):237-251.
[71] Kuruvilla ME, Lee FE, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol 2019;56(2):219-233.

[72] Lakhan SE, Sheafer H, Tepper D. The Effectiveness of Aromatherapy in Reducing Pain: A Systematic Review and Meta-Analysis. Pain research and treatment 2016;2016:8158693.
[73] Lam TH, Chung KF, Lee CT, Yeung WF, Yu BY. Hypnotherapy for insomnia: A randomized controlled trial comparing generic and disease-specific suggestions. Complement Ther Med 2018;41:231-239.
[74] Lavigne GJ, Herrero Babiloni A, Beetz G, Dal Fabbro C, Sutherland K, Huynh N, Cistulli PA. Critical Issues in Dental and Medical Management of Obstructive Sleep Apnea. Journal of dental research 2020;99(1):26-35.
[75] LeBlanc M, Merette C, Savard J, Ivers H, Baillargeon L, Morin CM. Incidence and risk factors of insomnia in a population-based sample. Sleep 2009;32(8):1027-1037.
[76] Lee C, Crawford C, Hickey A, Active Self-Care Therapies for Pain Working G. Mind-body therapies for the self-management of chronic pain symptoms. Pain medicine 2014;15 Suppl 1:S21-39.
[77] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipovic SR, Grefkes C, Hasan A, Hummel FC, Jaaskelainen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorova I, Rossi S, Sahlsten H, Schecklmann M, Szekely D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2019.
[78] Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, Cotelli M, De Ridder D, Ferrucci R, Langguth B, Marangolo P, Mylius V, Nitsche MA, Padberg F, Palm U, Poulet E, Priori A, Rossi S, Schecklmann M, Vanneste S, Ziemann U, Garcia-Larrea L, Paulus W. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2017;128(1):56-92.
[79] Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain 2012;13(10):936-944.
[80] Lim DC, Mazzotti DR, Sutherland K, Mindel JW, Kim J, Cistulli PA, Magalang UJ, Pack AI, de Chazal P, Penzel T, Investigators S. Reinventing polysomnography in the age of precision medicine. Sleep medicine reviews 2020;52:101313.
[81] Lo HS, Yang CM, Lo HG, Lee CY, Ting H, Tzang BS. Treatment effects of gabapentin for primary insomnia. Clin Neuropharmacol 2010;33(2):84-90.
[82] Loggia ML, Berna C, Kim J, Cahalan CM, Gollub RL, Wasan AD, Harris RE, Edwards RR, Napadow V. Disrupted brain circuitry for pain-related reward/punishment in fibromyalgia. Arthritis Rheumatol 2014;66(1):203-212.
[83] Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. The Cochrane database of systematic reviews 2014(1):CD007115.
[84] Maixner W, Greenspan JD, Dubner R, Bair E, Mulkey F, Miller V, Knott C, Slade GD, Ohrbach R, Diatchenko L, Fillingim RB. Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain 2011;12(11 Suppl):T75-91.
[85] Marshall L, Helgadottir H, Molle M, Born J. Boosting slow oscillations during sleep potentiates memory. Nature 2006;444(7119):610-613.
[86] Marshall L, Molle M, Hallschmid M, Born J. Transcranial direct current stimulation during sleep improves declarative memory. The Journal of neuroscience : the official journal of the Society for Neuroscience 2004;24(44):9985-9992.

[87] Mateu M, Alda O, Inda MD, Margarit C, Ajo R, Morales D, van-der Hofstadt CJ, Peiro AM. Randomized, Controlled, Crossover Study of Self-administered Jacobson Relaxation in Chronic, Nonspecific, Low-back Pain. Altern Ther Health Med 2018;24(6):22-30.
[88] Mathias JL, Cant ML, Burke ALJ. Sleep disturbances and sleep disorders in adults living with chronic pain: a meta-analysis. Sleep medicine 2018.
[89] Matthews EE, Arnedt JT, McCarthy MS, Cuddihy LJ, Aloia MS. Adherence to cognitive behavioral therapy for insomnia: a systematic review. Sleep medicine reviews 2013;17(6):453-464.
[90] Mayer P, Herrero Babiloni A, Aube JL, Kaddaha Z, Marshansky S, Rompre PH, Jobin V, Lavigne GJ. Autonomic Arousals as Surrogates for Cortical Arousals Caused by Respiratory Events: A Methodological Optimization Study in the Diagnosis of Sleep Breathing Disorders. Nature and science of sleep 2019;11:423-431.
[91] McCrae CS, Williams J, Roditi D, Anderson R, Mundt JM, Miller MB, Curtis AF, Waxenberg LB, Staud R, Berry RB, Robinson ME. Cognitive behavioral treatments for insomnia (CBT-I) and pain (CBT-P) in adults with comorbid chronic insomnia and fibromyalgia: Clinical outcomes from the SPIN randomized controlled trial. Sleep 2018.
[92] Miglis MG. Autonomic dysfunction in primary sleep disorders. Sleep medicine 2016;19:40-49.
[93] Miller L, Ohlman T, Naugle KM. Sensitivity to Physical Activity Predicts Daily Activity Among Pain-Free Older Adults. Pain medicine 2018;19(8):1683-1692.
[94] Moana-Filho EJ, Herrero Babiloni A. Endogenous pain modulation in chronic temporomandibular disorders: Derivation of pain modulation profiles and assessment of its relationship with clinical characteristics. J Oral Rehabil 2019;46(3):219-232.
[95] Moana-Filho EJ, Herrero Babiloni A, Nisley A. Endogenous pain modulation assessed with offset analgesia is not impaired in chronic temporomandibular disorder pain patients. J Oral Rehabil 2019;46(11):1009-1022.
[96] Moldofsky H, Harris HW, Archambault WT, Kwong T, Lederman S. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. The Journal of rheumatology 2011;38(12):2653-2663.
[97] Morin CM. Cognitive-behavioral approaches to the treatment of insomnia. The Journal of clinical psychiatry 2004;65 Suppl 16:33-40.
[98] Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. Pain 1999;80(1-2):1-13.
[99] Muehlbacher M, Nickel MK, Kettler C, Tritt K, Lahmann C, Leiberich PK, Nickel C, Krawczyk J, Mitterlehner FO, Rother WK, Loew TH, Kaplan P. Topiramate in treatment of patients with chronic low back pain: a randomized, double-blind, placebo-controlled study. Clin J Pain 2006;22(6):526-531.
[100] Murakami M, Fox L, Dijkers MP. Ear Acupuncture for Immediate Pain Relief-A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain medicine 2017;18(3):551-564.
[101] Myhr G, Payne K. Cost-effectiveness of cognitive-behavioural therapy for mental disorders: implications for public health care funding policy in Canada. Canadian journal of psychiatry Revue canadienne de psychiatrie 2006;51(10):662-670.
[102] Nardone R, Sebastianelli L, Versace V, Brigo F, Golaszewski S, Pucks-Faes E, Saltuari L, Trinka E. Effects of repetitive transcranial magnetic stimulation in subjects with sleep disorders. Sleep medicine 2020;71:113-121.
[103] Nardone R, Sebastianelli L, Versace V, Brigo F, Golaszewski S, Pucks-Faes E, Saltuari L, Trinka E. Effects of repetitive transcranial magnetic stimulation in subjects with sleep disorders. Sleep medicine 2020.

[104] Nijs J, Mairesse O, Neu D, Leysen L, Danneels L, Cagnie B, Meeus M, Moens M, Ickmans K, Goubert D. Sleep Disturbances in Chronic Pain: Neurobiology, Assessment, and Treatment in Physical Therapist Practice. Physical therapy 2018;98(5):325-335.
[105] Nord CL, Halahakoon DC, Limbachya T, Charpentier C, Lally N, Walsh V, Leibowitz J, Pilling S, Roiser JP. Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2019;44(9):1613-1622.
[106] O'Brien EM, Waxenberg LB, Atchison JW, Gremillion HA, Staud RM, McCrae CS, Robinson ME. Negative mood mediates the effect of poor sleep on pain among chronic pain patients. Clin J Pain 2010;26(4):310-319.
[107] O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. The Cochrane database of systematic reviews 2014(4):CD008208.
[108] Palm U, Chalah MA, Padberg F, Al-Ani T, Abdellaoui M, Sorel M, Dimitri D, Creange A, Lefaucheur JP, Ayache SS. Effects of transcranial random noise stimulation (tRNS) on affect, pain and attention in multiple sclerosis. Restorative neurology and neuroscience 2016;34(2):189-199.
[109] Papalambros NA, Weintraub S, Chen T, Grimaldi D, Santostasi G, Paller KA, Zee PC, Malkani RG. Acoustic enhancement of sleep slow oscillations in mild cognitive impairment. Ann Clin Transl Neurol 2019;6(7):1191-1201.
[110] Passos GS, Poyares D, Santana MG, D'Aurea CV, Youngstedt SD, Tufik S, de Mello MT. Effects of moderate aerobic exercise training on chronic primary insomnia. Sleep medicine 2011;12(10):1018-1027.
[111] Pavlova M, Ference J, Hancock M, Noel M. Disentangling the Sleep-Pain Relationship in Pediatric Chronic Pain: The Mediating Role of Internalizing Mental Health Symptoms. Pain research & management 2017;2017:1586921.
[112] Pei Q, Wu B, Tang Y, Yang X, Song L, Wang N, Li Y, Sun C, Ma S, Ni J. Repetitive Transcranial Magnetic Stimulation at Different Frequencies for Postherpetic Neuralgia: A Double-Blind, Sham-Controlled, Randomized Trial. Pain physician 2019;22(4):E303-e313.
[113] Piovezan RD, Kase C, Moizinho R, Tufik S, Poyares D. Gabapentin acutely increases the apnea-hypopnea index in older men: data from a randomized, double-blind, placebo-controlled study. Journal of sleep research 2017;26(2):166-170.
[114] Polli A, Godderis L, Ghosh M, Ickmans K, Nijs J. Epigenetic and miRNA expression changes in people with pain: a systematic review. The journal of pain : official journal of the American Pain Society 2019.
[115] Ritterband LM, Thorndike FP, Gonder-Frederick LA, Magee JC, Bailey ET, Saylor DK, Morin CM. Efficacy of an Internet-based behavioral intervention for adults with insomnia. Arch Gen Psychiatry 2009;66(7):692-698.
[116] Rizzi M, Radovanovic D, Santus P, Airoldi A, Frassanito F, Vanni S, Cristiano A, Masala IF, Sarzi-Puttini P. Influence of autonomic nervous system dysfunction in the genesis of sleep disorders in fibromyalgia patients. Clinical and experimental rheumatology 2017;35 Suppl 105(3):74-80.
[117] Roberts DM, Schade MM, Mathew GM, Gartenberg D, Buxton OM. Detecting Sleep Using Heart Rate and Motion Data from Multisensor Consumer-Grade Wearables, Relative to Wrist Actigraphy and Polysomnography. Sleep 2020.
[118] Roizenblatt S, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, Tufik S, Boggio PS, Valle AC. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain Pract 2007;7(4):297-306.

[119] Roth T, Arnold LM, Garcia-Borreguero D, Resnick M, Clair AG. A review of the effects of pregabalin on sleep disturbance across multiple clinical conditions. Sleep medicine reviews 2014;18(3):261-271.
[120] Rusch HL, Rosario M, Levison LM, Olivera A, Livingston WS, Wu T, Gill JM. The effect of mindfulness meditation on sleep quality: a systematic review and meta-analysis of randomized controlled trials. Annals of the New York Academy of Sciences 2019;1445(1):5-16.
[121] Seminowicz DA, Remeniuk B, Krimmel SR, Smith MT, Barrett FS, Wulff AB, Furman AJ, Geuter S, Lindquist MA, Irwin MR, Finan PH. Pain-related nucleus accumbens function: modulation by reward and sleep disruption. Pain 2019;160(5):1196-1207.
[122] Simpson NS, Scott-Sutherland J, Gautam S, Sethna N, Haack M. Chronic exposure to insufficient sleep alters processes of pain habituation and sensitization. Pain 2018;159(1):33-40.
[123] Singareddy R, Vgontzas AN, Fernandez-Mendoza J, Liao D, Calhoun S, Shaffer ML, Bixler EO. Risk factors for incident chronic insomnia: a general population prospective study. Sleep medicine 2012;13(4):346-353.
[124] Smith MT, Jr., Remeniuk B, Finan PH, Speed TJ, Tompkins DA, Robinson M, Gonzalez K, Bjurstrom MF, Irwin MR. Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: Implications for sex differences in chronic pain. Sleep 2018.
[125] Spaeth M, Bennett RM, Benson BA, Wang YG, Lai C, Choy EH. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: results of an international phase 3 trial. Annals of the rheumatic diseases 2012;71(6):935-942.
[126] Staffe AT, Bech MW, Clemmensen SLK, Nielsen HT, Larsen DB, Petersen KK. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants. PloS one 2019;14(12):e0225849.
[127] Strafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. Brain : a journal of neurology 2003;126(Pt 12):2609-2615.
[128] Straube S, Derry S, Moore RA, McQuay HJ. Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports. Rheumatology 2010;49(4):706-715.
[129] Tang NK, Lereya ST, Boulton H, Miller MA, Wolke D, Cappuccio FP. Nonpharmacological Treatments of Insomnia for Long-Term Painful Conditions: A Systematic Review and Meta-analysis of Patient-Reported Outcomes in Randomized Controlled Trials. Sleep 2015;38(11):1751-1764.
[130] Tang NKY. Cognitive behavioural therapy in pain and psychological disorders: Towards a hybrid future. Prog Neuropsychopharmacol Biol Psychiatry 2018;87(Pt B):281-289.
[131] Tang NKY, Moore C, Parsons H, Sandhu HK, Patel S, Ellard DR, Nichols VP, Madan J, Collard VEJ, Sharma U, Underwood M. Implementing a hybrid cognitive-behavioural therapy for pain-related insomnia in primary care: lessons learnt from a mixed-methods feasibility study. BMJ Open 2020;10(3):e034764.
[132] Tang NKY, Stella MT, Banks PDW, Sandhu HK, Berna C. The effect of opioid therapy on sleep quality in patients with chronic non-malignant pain: A systematic review and exploratory meta-analysis. Sleep medicine reviews 2019;45:105-126.
[133] Taranto-Montemurro L, Messineo L, Wellman A. Targeting Endotypic Traits with Medications for the Pharmacological Treatment of Obstructive Sleep Apnea. A Review of the Current Literature. Journal of clinical medicine 2019;8(11).
[134] Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. Arthritis and rheumatism 2004;51(1):9-13.

[135] Trauer JM, Qian MY, Doyle JS, Rajaratnam SM, Cunnington D. Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review and Meta-analysis. Annals of internal medicine 2015;163(3):191-204.
[136] Valim V, Natour J, Xiao Y, Pereira AF, Lopes BB, Pollak DF, Zandonade E, Russell IJ. Effects of physical exercise on serum levels of serotonin and its metabolite in fibromyalgia: a randomized pilot study. Rev Bras Reumatol 2013;53(6):538-541.
[137] Van Ryswyk E, Antic NA. Opioids and Sleep-Disordered Breathing. Chest 2016;150(4):934-944.
[138] Venugopal R, Sasidharan A, Marigowda V, Kumar G, Nair AK, Sharma S, Mukundan CS, Kutty BM. Beyond Hypnograms: Assessing Sleep Stability Using Acoustic and Electrical Stimulation. Neuromodulation 2019;22(8):911-915.
[139] Volkow ND, Tomasi D, Wang GJ, Telang F, Fowler JS, Logan J, Benveniste H, Kim R, Thanos PK, Ferre S. Evidence that sleep deprivation downregulates dopamine D2R in ventral striatum in the human brain. The Journal of neuroscience : the official journal of the Society for Neuroscience 2012;32(19):6711-6717.
[140] Wang HX, Wang L, Zhang WR, Xue Q, Peng M, Sun ZC, Li LP, Wang K, Yang XT, Jia Y, Zhou QL, Xu ZX, Li N, Dong K, Zhang Q, Song HQ, Zhan SQ, Min BQ, Fan CQ, Zhou AH, Guo XH, Li HB, Liang LR, Yin L, Si TM, Huang J, Yan TY, Cosci F, Kamiya A, Lu J, Wang YP. Effect of Transcranial Alternating Current Stimulation for the Treatment of Chronic Insomnia: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Clinical Trial. Psychotherapy and psychosomatics 2020;89(1):38-47.
[141] Wang X, Li P, Pan C, Dai L, Wu Y, Deng Y. The Effect of Mind-Body Therapies on Insomnia: A Systematic Review and Meta-Analysis. Evidence-based complementary and alternative medicine : eCAM 2019;2019:9359807.
[142] Whibley D, AlKandari N, Kristensen K, Barnish M, Rzewuska M, Druce KL, Tang NKY. Sleep and Pain: A Systematic Review of Studies of Mediation. Clin J Pain 2019.
[143] Wiffen PJ, Derry S, Bell RF, Rice AS, Tolle TR, Phillips T, Moore RA. Gabapentin for chronic neuropathic pain in adults. The Cochrane database of systematic reviews 2017;6:CD007938.
[144] Williams AC, Eccleston C, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. The Cochrane database of systematic reviews 2012;11:CD007407.
[145] Winkelman JW, Wipper B, Purks J, Mei L, Schoerning L. Topiramate reduces nocturnal eating in sleep-related eating disorder. Sleep 2020.
[146] Winslow DH, Bowden CH, DiDonato KP, McCullough PA. A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. Sleep 2012;35(11):1529-1539.
[147] Yang PY, Ho KH, Chen HC, Chien MY. Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review. J Physiother 2012;58(3):157-163.
[148] Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain 2015;156 Suppl 1:S24-31.
[149] Ye YY, Zhang YF, Chen J, Liu J, Li XJ, Liu YZ, Lang Y, Lin L, Yang XJ, Jiang XJ. Internet-Based Cognitive Behavioral Therapy for Insomnia (ICBT-i) Improves Comorbid Anxiety and Depression-A Meta-Analysis of Randomized Controlled Trials. PloS one 2015;10(11):e0142258.
[150] Yuan QL, Wang P, Liu L, Sun F, Cai YS, Wu WT, Ye ML, Ma JT, Xu BB, Zhang YG. Acupuncture for musculoskeletal pain: A meta-analysis and meta-regression of sham-controlled randomized clinical trials. Scientific reports 2016;6:30675.

[151] Zandvakili A, Philip NS, Jones SR, Tyrka AR, Greenberg BD, Carpenter LL. Use of machine learning in predicting clinical response to transcranial magnetic stimulation in comorbid posttraumatic stress disorder and major depression: A resting state electroencephalography study. Journal of affective disorders 2019;252:47-54.

Figure 1

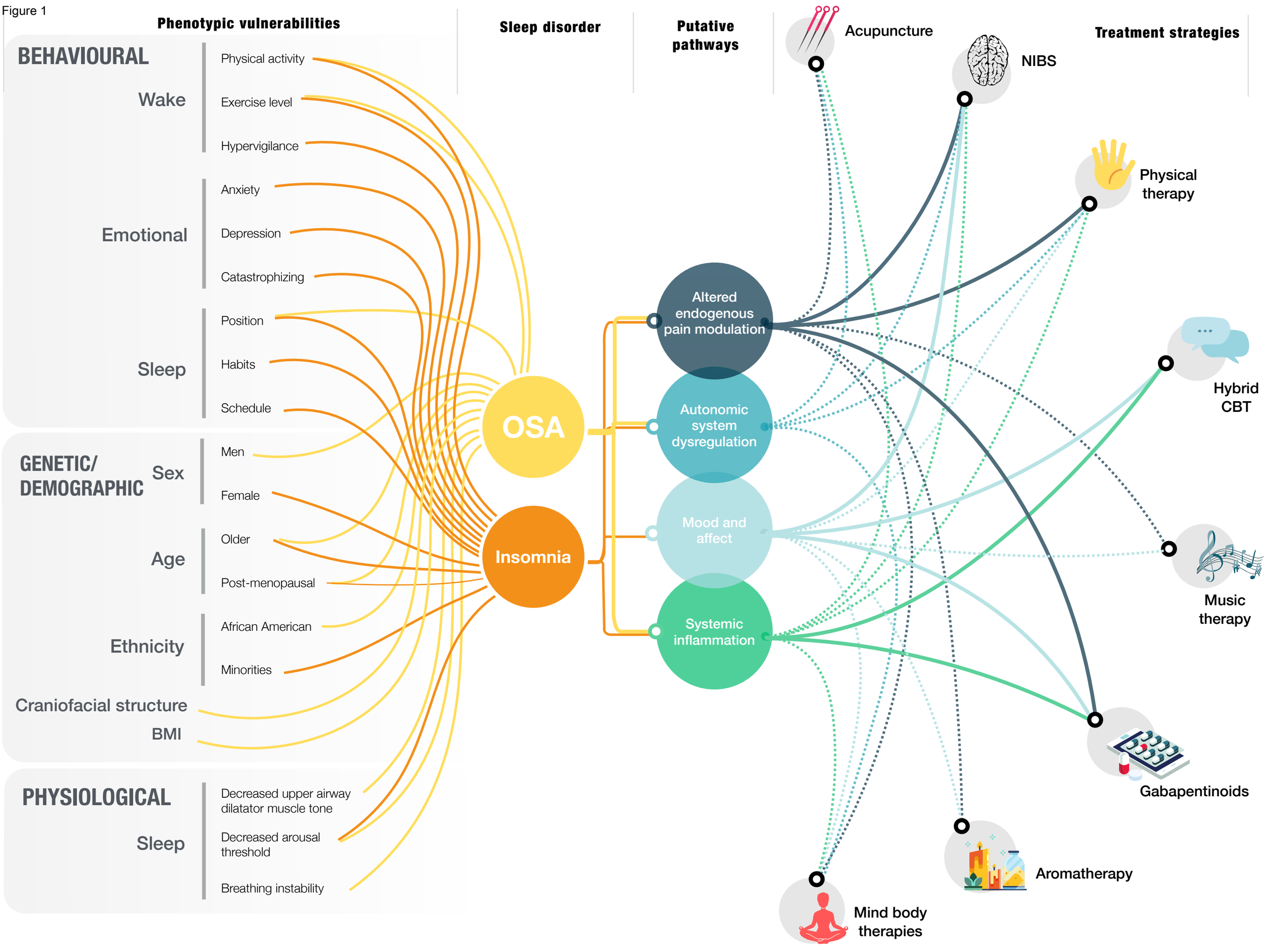
Phenotypic vulnerabilities
Sleep disorder
Putative pathways
Treatment strategies
BEHAVIOURAL
Wake
Physical activity
Exercise level
Hypervigilance
Emotional
Anxiety
Depression
Catastrophizing
Sleep
Position
Habits
Schedule
GENETIC/ DEMOGRAPHIC
Sex
Men
Female
Age
Older
Post-menopausal
Ethnicity
African American
Minorities
Craniofacial structure
BMI
PHYSIOLOGICAL
Sleep
Decreased upper airway dilatator muscle tone
Decreased arousal threshold
Breathing instability
OSA
Insomnia
Altered endogenous pain modulation
Autonomic system dysregulation
Mood and affect
Systemic inflammation
Acupuncture
NIBS
Physical therapy
Hybrid CBT
Music therapy
Gabapentinoids
Aromatherapy
Mind body therapies

Figure 2


Brain imaging
Conditionned pain modulation
Polysomnography
Comorbid disease
Central sensitization
Breathing disability
Pain condition
Sleep microstructure
Sleep macrostructure
Genetics
Offset analgesia
Quantitative sensory testing
Arousals
Temporal summation
Motor evoked potentials
Electroencephalography
Treatment response
Autonomic markers
Cortical excitability
Sleepstability
Risk factors
Actigraphy

[104] Nijs J, Mairesse O, Neu D, Leysen L, Danneels L, Cagnie B, Meeus M, Moens M, Ickmans K, Goubert D. Sleep Disturbances in Chronic Pain: Neurobiology, Assessment, and Treatment in Physical Therapist Practice. Physical therapy 2018;98(5):325-335.
[105] Nord CL, Halahakoon DC, Limbachya T, Charpentier C, Lally N, Walsh V, Leibowitz J, Pilling S, Roiser JP. Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology 2019;44(9):1613-1622.
[106] O'Brien EM, Waxenberg LB, Atchison JW, Gremillion HA, Staud RM, McCrae CS, Robinson ME. Negative mood mediates the effect of poor sleep on pain among chronic pain patients. Clin J Pain 2010;26(4):310-319.
[107] O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. The Cochrane database of systematic reviews 2014(4):CD008208.
[108] Palm U, Chalah MA, Padberg F, Al-Ani T, Abdellaoui M, Sorel M, Dimitri D, Creange A, Lefaucheur JP, Ayache SS. Effects of transcranial random noise stimulation (tRNS) on affect, pain and attention in multiple sclerosis. Restorative neurology and neuroscience 2016;34(2):189-199.
[109] Papalambros NA, Weintraub S, Chen T, Grimaldi D, Santostasi G, Paller KA, Zee PC, Malkani RG. Acoustic enhancement of sleep slow oscillations in mild cognitive impairment. Ann Clin Transl Neurol 2019;6(7):1191-1201.
[110] Passos GS, Poyares D, Santana MG, D'Aurea CV, Youngstedt SD, Tufik S, de Mello MT. Effects of moderate aerobic exercise training on chronic primary insomnia. Sleep medicine 2011;12(10):1018-1027.
[111] Pavlova M, Ference J, Hancock M, Noel M. Disentangling the Sleep-Pain Relationship in Pediatric Chronic Pain: The Mediating Role of Internalizing Mental Health Symptoms. Pain research & management 2017;2017:1586921.
[112] Pei Q, Wu B, Tang Y, Yang X, Song L, Wang N, Li Y, Sun C, Ma S, Ni J. Repetitive Transcranial Magnetic Stimulation at Different Frequencies for Postherpetic Neuralgia: A Double-Blind, Sham-Controlled, Randomized Trial. Pain physician 2019;22(4):E303-e313.
[113] Piovezan RD, Kase C, Moizinho R, Tufik S, Poyares D. Gabapentin acutely increases the apnea-hypopnea index in older men: data from a randomized, double-blind, placebo-controlled study. Journal of sleep research 2017;26(2):166-170.
[114] Polli A, Godderis L, Ghosh M, Ickmans K, Nijs J. Epigenetic and miRNA expression changes in people with pain: a systematic review. The journal of pain : official journal of the American Pain Society 2019.
[115] Ritterband LM, Thorndike FP, Gonder-Frederick LA, Magee JC, Bailey ET, Saylor DK, Morin CM. Efficacy of an Internet-based behavioral intervention for adults with insomnia. Arch Gen Psychiatry 2009;66(7):692-698.
[116] Rizzi M, Radovanovic D, Santus P, Airoldi A, Frassanito F, Vanni S, Cristiano A, Masala IF, Sarzi-Puttini P. Influence of autonomic nervous system dysfunction in the genesis of sleep disorders in fibromyalgia patients. Clinical and experimental rheumatology 2017;35 Suppl 105(3):74-80.
[117] Roberts DM, Schade MM, Mathew GM, Gartenberg D, Buxton OM. Detecting Sleep Using Heart Rate and Motion Data from Multisensor Consumer-Grade Wearables, Relative to Wrist Actigraphy and Polysomnography. Sleep 2020.
[118] Roizenblatt S, Fregni F, Gimenez R, Wetzel T, Rigonatti SP, Tufik S, Boggio PS, Valle AC. Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study. Pain Pract 2007;7(4):297-306.

Towards the endotyping of the sleep-pain interaction: a topical review on multitarget strategies based on phenotypic vulnerabilities and putative pathways

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